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First Total Synthesis of Isoprostane $IPF_{2\alpha}$-III

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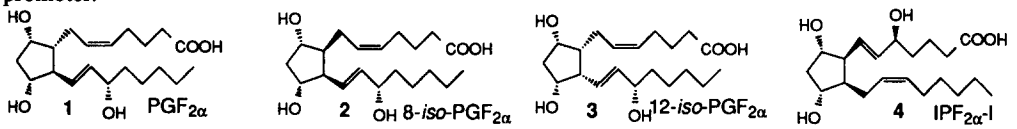
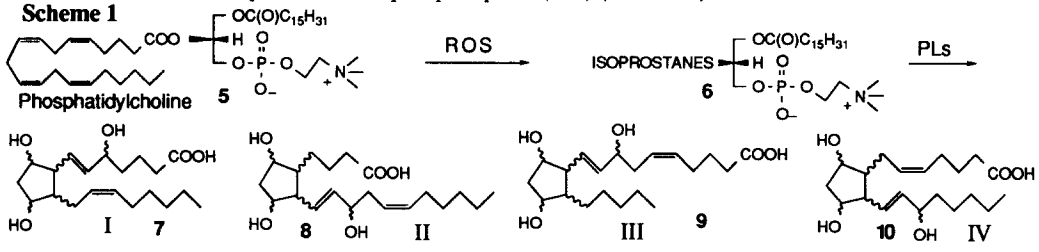
Abstract: The first total synthesis of $IPF_{2\alpha}$-III, a type III isoprostane is described using a *syn-anti-syn* lactone **34** prepared from D-glucose and a novel iodohydrin synthon **30**. This is first synthesis of a representative of type III isoprostane which is anticipated to be formed *in vivo* from arachidonic acid by free-radical mechanism. This synthetic material will help elucidate the formation *in vivo* of type III isoprostanes. © 1997 Elsevier Science Ltd.

Clinical studies have raised the possibility that Vitamin E supplementation diminishes the incidence of cardiovascular diseases.[1] Vitamin E (α-tocopherol), a free radical inhibitor/scavenger, is the principal lipid soluble antioxidant in plasma, in low density lipoprotein (LDL), and phospholipids which are major constituents of cell membranes.[2] The implications of such observations are that free radicals (e.g., HO·, $O_2^{\cdot-}$, ROO·) are involved in cardiovascular diseases (e.g., atherosclerosis, myocardial infarction, etc.).[3,4] Free radicals have also been implicated in alcohol induced liver diseases and α-hydroxy ethyl radicals have been proposed as free radical promoter.[5]



Recently, a new class of natural products, the isoprostanes (IP), have been described.[6-8] We have reported the total syntheses of 8-*iso*-$PGF_{2\alpha}$ **2**, *ent*-8-*iso*-$PGF_{2\alpha}$, 12-*iso*-$PGF_{2\alpha}$ **3**, and $IPF_{2\alpha}$-I **4**.[7,9,10] These isoprostanes, isomeric with biologically active prostaglandins (PGs), are produced *in vivo* by a cyclooxygenase (COX) independent free-radical mechanism. Note the *cis* configuration of the side chains of IPs (**2**, **3**, and **4**) as compared to the *trans* relationship found in PGs (e.g., $PGF_{2\alpha}$ **1**). The isoprostanes, formed *in situ* on phospholipids by peroxidation of unsaturated fatty acids such as arachidonic acid (AA), are subsequently released in the free form by the action of phospholipases (PLs) (Scheme 1). Based on chemical considerations,

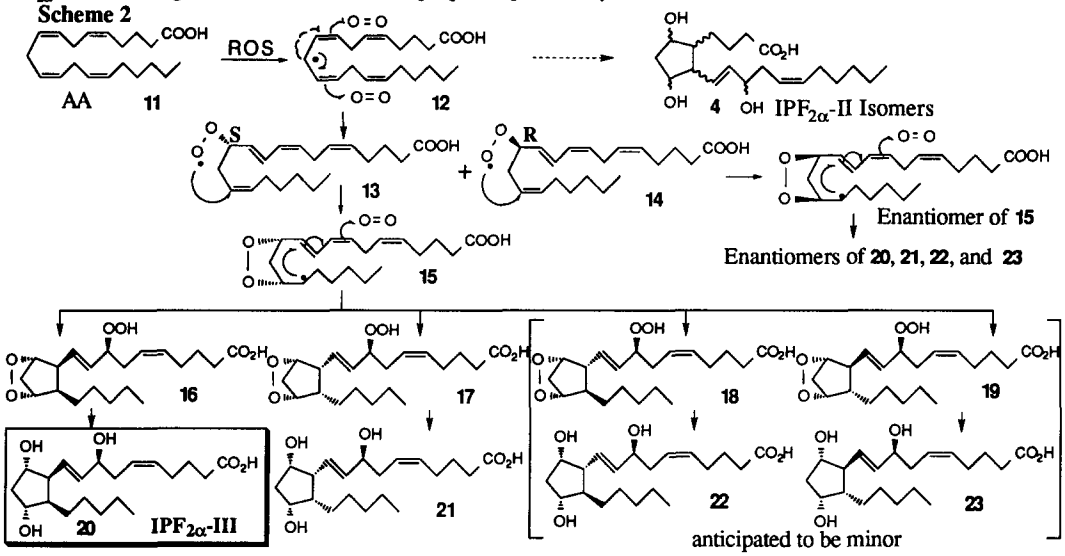
Scheme 1



four groups of isoprostanes (I-IV) have been proposed as potential products of reactive oxygen species (ROS)-initiated peroxidation of AA.[6-8] One of these isoprostanes, 8-*iso*-$PGF_{2\alpha}$, is a potent vasoconstrictor and has been identified in minor amounts in the COX-1 and COX-2 induced oxygenation of AA.[11,12] This is of importance due to the recent development of selective COX-2 inhibitors as antiinflammatory agents.[13,14]

The synthesis of $IPF_{2\alpha}$-III **20** which we report here, is part of our overall plans to check if indeed the four classes of compounds proposed in Scheme 1 are formed *in vivo*. We were particularly encouraged in this strategy by the successful identification of $IPF_{2\alpha}$-I from class I as a major isoprostane in urine, hence validating the existense of several classes of isoprostanes.[10] Our proposed mechanism for the formation of isoprostanes type III including $IPF_{2\alpha}$-III from AA by a free radical peroxidation process is depicted in Scheme 2. The radical formed at C_{10} can give rise to $IPF_{2\alpha}$-III as well as $IPF_{2\alpha}$-II isomers. We have named this novel isoprostane, $IPF_{2\alpha}$-III according to the nomenclature we proposed previously.[10]

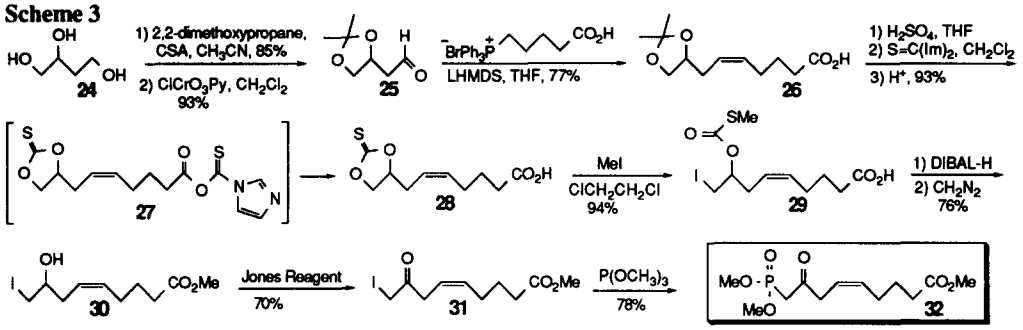
Scheme 2



We opted for a convergent synthesis in which the top and more elaborate side chain in **20** would be introduced last in the synthesis. Synthon **32** was selected and prepared using our recently developed methodology for the preparation of iodohydrins.[15] The reason we selected iodohydrin is to ensure milder conditions in the preparation of the phosphonate **32**. 1,2,4-butanetriol **24** was converted to the aldehyde **25** in two steps by the treatment of 2,2-dimethoxypropane in the presence of camphor sulfonic acid and then pyridinium chlorochromate oxidation in methylene chloride at room temperature in 79% yield from **24**. The Wittig reaction with commercial (4-carboxybutyl)triphenylphosphonium bromide (1.3 equiv.) and lithium hexamethyldisilazane (2.3 equiv.) in THF at -78 °C gave the *cis* olefin **26** in 77% yield. After removal of the 8,9-isopropylidene group in **26** with 4% aqueous H_2SO_4, 8,9-dihydroxy-non-5-enoic acid was treated with thiocarbonylbis(imidazole) in methylene chloride at room temperature to afford the thionocarbonate **28** in 93% yield from **26**. Treatment of the thionocarbonate **28** with methyl iodide in 1,2-dichloroethane at reflux afforded the iodo thiocarbonate **29** in 94% yield. The reduction of the methylthiocarbonyl group in **29** with DIBAL-H in methylene chloride at -78 °C , followed by an acidic work-up and diazomethane treatment furnished the iodohydrin **30** in 76% yield. Oxidation of the alcohol group in **30** with Jones Reagent gave the β-keto iodide in

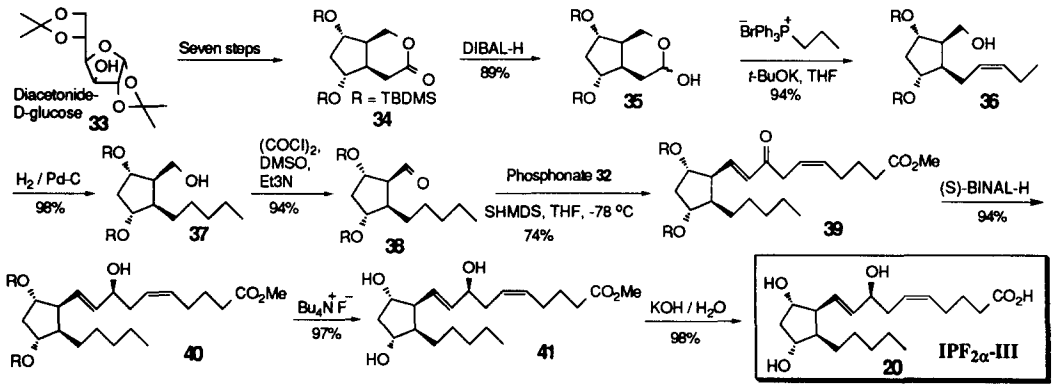
70% yield. Finally, treatment of the β-keto iodide **31** with trimethylphosphite in acetonitrile at room temperature afforded the β-ketophosphonate **32** in 78% yield.

Scheme 3

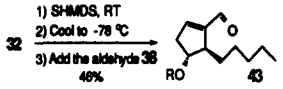


The other key intermediate *syn-anti-syn* lactone **34** for the synthesis of $IPF_{2\alpha}$-III was prepared from diacetonide-D-glucose in seven steps as reported earlier.[10] The reduction of lactone **34** with DIBAL-H in methylene chloride at -78 °C, followed by acidic work-up, afforded a mixture of lactol epimers **35** in 89% yield, which was used as such in the next step. The Wittig reaction with commercial propyltriphenylphosphonium bromide (5 equiv.) and potassium t-butoxide (4.7 equiv.) at 0 °C proceeded smoothly to give the *cis* olefin **36** in 94% yield. Saturation of the olefin in **36** was performed by palladium/carbon catalyzed hydrogenation at atmospheric pressure to give **37** in 98% yield. The Swern oxidation of the alcohol **37** using oxalyl chloride, DMSO, and triethylamine yielded aldehyde **38** in 94% yield. Horner-Emmons reaction of the aldehyde **38** to introduce the upper side chain using the anion of β-ketophosphonate **32** generated with sodium *bis*(trimethylsilyl)amide in THF at -78 °C, afforded the enone **39** in 74% yield.[16] The enantioselective reduction of the C_8 keto group in **39** with chiral reducing agent (S)-BINAL-H[17] proceeded well and afforded the desired pure 8(S) derivative **40** in 94% yield. The deprotection of the *bis*-silyl groups in **40** was carried out using tetrabutylammonium fluoride in THF at room temperature to afford $IPF_{2\alpha}$-III methyl ester **41** in 97% yield. Finally, the basic hydrolysis of **41** with aqueous potassium hydroxide in dioxane at room temperature yielded the desired $IPF_{2\alpha}$-III **20** in 98% yield.[18]

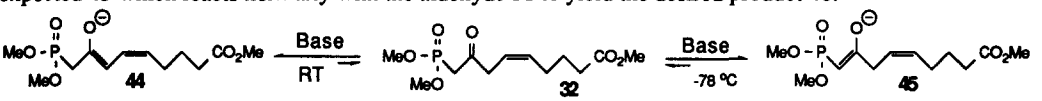
Scheme 4



When we first performed the Horner-Emmons reaction on the aldehyde **38**, we generated the anion of **32** at room temperature then cooled to -78 °C, and added aldehyde **38**. Under these conditions, the α,β unsaturated aldehyde **43** was the major product of the reaction.



One way to explain the difference in reactivity of the phosphonate anion generated at RT and then cooled to -78 °C versus the anion generated at -78 °C is as follows. It is possible that at RT an anion such as **44** is formed preferencially. This anion will act strictly as a base. On the other hand the anion generated at -78 °C is the expected **45** which reacts normally with the aldehyde **38** to yield the desired product **40**.



Availability of $IPF_{2\alpha}$-III as a representative of type III isoprostanes will help us evaluate its biological properties and to check its formation *in vivo* on phospholipids and in biological fluids.

ACKNOWLEDGMENTS: We wish to thank the NIH for support under Grant DK-44730 (J. R.), SCOR Grant HL 54500 (G. A. F.), the NSF for an AMX-360 NMR instrument (Grant CHE-90-13145), and the Turkish Ministry of Education for the doctoral fellowship to M. A.

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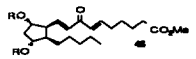
16. This somewhat reduced yield is due to the formation of **46** in 15% yield. 
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18. Spectral data for the $IPF_{2\alpha}$-III: ^{1}H NMR (CD_3COCD_3): δ 5.5 (dd, *J* = 6.4 and 15.7 Hz, 1H), 5.4 (m, 2H), 5.1 (dt, *J* = 6.0 and 11.9 Hz, 1H), 3.9 (m, 1H), 3.8 (dt, *J* = 6.8 and 13 Hz, 1H), 2.6 (m, 1H), 2.4 (dt, J = 7.2, 14.2 Hz, 1H), 2.3 (t, *J* = 7.4 Hz, 2H), 2.25 (m, 2H), 2.1 (m, 3H), 1.6 (dt, *J* = 7.4 and 14.8 Hz, 2H), 1.5 (m, 1H), 1.4-1.2 (m, 8H), 0.9 (t, *J* = 6.8 Hz, 3H). ^{13}C NMR (CD_3COCD_3): δ 174.7, 136.0, 131.1, 129.5, 127.8, 76.7, 76.4, 72.5, 54.1, 50.5, 44.2, 36.6, 33.7, 33.0, 29.6, 28.7, 27.5, 25.7, 23.4, 14.5. ESI MS *m/z* calc for (M - 1) 353.2, found 353.2

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